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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,812	06/29/2001	Thomas D. Madden	16303-008030	6998

500 7590 10/03/2005

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,812	MADDEN ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,43 and 66-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 43, 66-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 7-11-05 is acknowledged.

Claims included in the prosecution are 36, 43, 66-68.

In view of the amendments, the double patenting rejection and the rejections over Madden are withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 36, 43 and 66-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) in combination with Webb (5,543,152).

Kirpotin as also pointed out in the previous action, discloses liposomal compositions wherein the active agent is in the precipitated form. The active agent according to Kirpotin can be any compound with ionizable groups. The active agents suggested by Kirpotin are antineoplastic agents, doxorubicin, vincristin, vinblastine and others. The liposomes are made of various phospholipids and sphingomyelin; the liposomes contain cholesterol. The lipid - drug ratios in Kirpotin also appear to fall within the claimed ratios (abstract; col. 4, line 54 through col. 6, line 18; col. 9, lines 22-67; examples and claims). Kirpotin's examples include only liposomes made from egg phosphatidylcholine and cholesterol in amounts falling within claimed ratios and not sphingomyelin; however, it would have been obvious to one of ordinary skill in the art to

use sphingomyelin instead of phospholipid in the liposomes since Kirpotin is suggestive of the use of sphingomyelin and provides guidance as to how to make these liposomes. The use of sphingomyelin along with cholesterol would also have been obvious to one of ordinary skill in the art since Webb teaches several advantages of liposomal formulations based on sphingomyelin and cholesterol (in instant amounts). According to Webb, these liposomes are much more stable to acid hydrolysis, significantly better drug retention characteristics, better loading characteristics into tumors and Webb teaches the applicability of the liposomes to a variety of lipophilic drugs, vinca alkaloids in particular (abstract, col. 4, line 18 through col. 5, line 34, examples and claims). Although both Kirpotin, and Webb lack the specific teachings of camptothecins, it would have been obvious to one of ordinary skill in the art to use any lipophilic drug including camptothecins with a reasonable expectation of success since both teach the applicability to lipophilic drugs and Webb in particular teaches the advantages which relate to liposomes containing sphingomyelin and cholesterol themselves.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that presently claimed invention is directed to specific liposomal vinorelbine composition having superior properties. Applicant further argues that the liposomal vinorelbine formulations having the claimed features possess superior pharmacokinetic properties, including slower drug release. In support, applicant points out to Fig. 1. Applicant state " Figure 1 shows that as the drug:lipid ratio is increased from 0.1: 1 to 0.2:1 to 0.3: 1, there is a corresponding increase in drug retention, which is. associated with drug precipitation in the liposomal interior.

Furthermore, there is a corresponding reduction in the blood clearance half-life for vinorelbine. As is understood in the art and described in the instant specification, a slower release rate and slower blood clearance half-life is preferable and more efficacious, particularly in the treatment of tumors, including those typically treated with vinorelbine. Thus, the claimed liposomal vinorelbine formulations, having a drug:lipid ratio of 0.1-0.5: 1 (w/w), such that at least 50% of the total vinorelbine is precipitated, are identified according to the instant specification, possess previously unrecognized advantages and, thus, are not obvious in light of the cited art". These arguments are not persuasive. First of all, it should be pointed out that though doxorubicin is used in the examples, on col. 6, line 18 Kirpotin clearly teaches the applicability of precipitation to vinca alkaloids, vinorelbine and vincristine. Through examples shows that the greater amounts of the drug are encapsulated in a precipitated state than the drug in unprecipitated state (129 nmoles/micromole phospholipid as opposed to 8 nmoles/ micromoles of phospholipid, see example 1). The increase in drug retention for vinorelbine is to be expected from Kirpotin's teachings and not an unexpected result. Secondly, the same claimed pharmacokinetic advantages of using SM/cholesterol in claimed ratios for vinca alkaloids are clearly evident from col. 9 of Webb. According to Webb, the leakage of vincristine from DSPC/chol. Is very rapid and in contrast its leakage from SM/chol. Liposomes was much slower, with a greater than 60 % of the entrapped drug remaining in the liposomes 24 hours after the injection. Therefore, what is observed by applicant is an expected result from the teachings of Kirpotin and Webb and not an unexpected finding.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

G S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK